which it pertains, or with which it is most nearly connected, to make and/or use the invention." Page 2 of the Office Action. The Examiner objected to the usage of certain terminologies and phrases in the claims, and, at the same time, kindly suggested ways of amending/restating those terminologies and phrases. Claims 1-23 and 26-31 were rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action, Page 5. Again, the Examiner kindly suggested alternate terminologies and phrases to overcome this rejection. Applicant has adopted the Examiner's suggestions and amended the claims as suggested by the Examiner, while appreciating the Examiner's suggestions. Applicant, therefore, respectfully requests withdrawal of the §112, first paragraph, and 112, second paragraph, rejections.

Claims 1-2 were rejected under 35 U.S.C. §102(b) as being anticipated by *Marchetti, Synlett.*, 1000-1002 (1999). The same claims were again rejected under 35 U.S.C. §102(b) as being anticipated by *Fossli* (U.S. 4,956,344). Claim 1 has been amended with provisos to exclude the cited compound of Marchetti and the cited compound of Fossli. Applicant, therefore, respectfully requests withdrawal of the two 102 anticipation rejections.

Applicant has added new claims 32-39 to claim certain methods of inhibition, again as kindly suggested by the Examiner on Page 4 of the Office Action.

There being no other rejections pending, Applicant believes that the claims, as amended, are in allowable condition and such an action is earnestly solicited. If the Examiner has any questions, the Examiner is invited to contact the undersigned.

Respectfully submitted,

June 18, 2003
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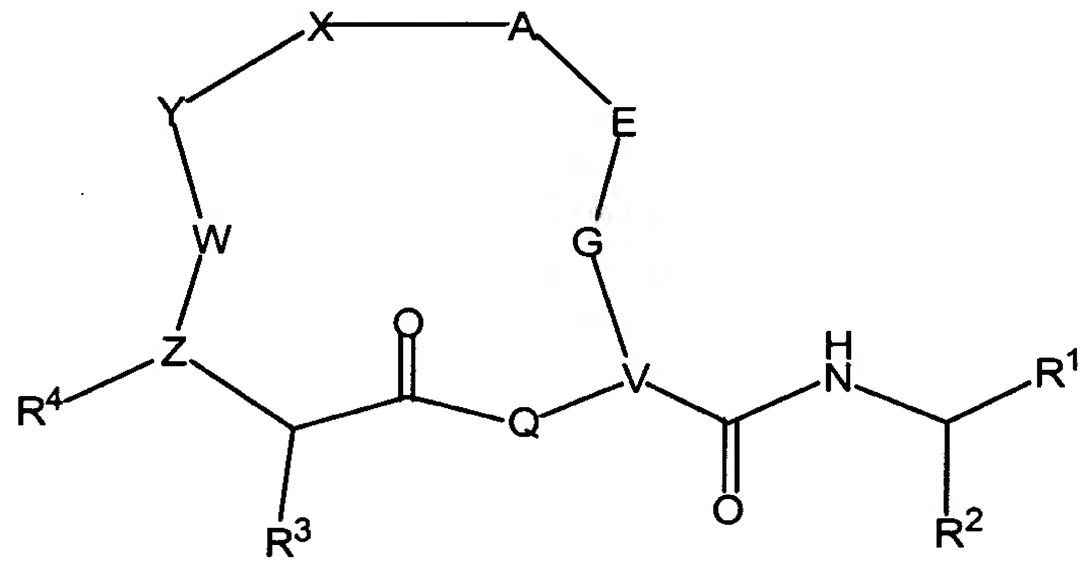
Marked Up Version of Amended Claims
(Added terms are underlined and deleted terms are in brackets)

Claim 1 (amended): A macrocyclic compound, [including] or enantiomers, stereoisomers, rotomers [and] or tautomers of said compound, [and] or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula I:



Formula I

wherein:

E, X and Y may be independently present or absent, and if present are independently selected from the moieties: alkyl, aryl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, aryl ether, alkyl amino, aryl amino, alkyl-aryl amino, alkyl sulfide, alkyl-aryl sulfide, aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, aryl sulfone, alkyl-alkyl sulfoxide, alkyl-aryl sulfoxide, alkyl amide, alkyl-aryl amide, aryl amide, alkyl sulfonamide, alkyl-aryl sulfonamide, aryl sulfonamide, alkyl urea, alkyl-aryl urea, aryl urea, alkyl carbamate, alkyl-aryl carbamate, aryl carbamate, alkyl -hydrazide, alkyl-aryl hydrazide, alkyl hydroxamide, alkyl-aryl hydroxamide, alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof, with the proviso that E, X and Y may optionally be additionally substituted with moieties selected from the group consisting of aromatic, alkyl, alkyl-aryl, heteroalkyl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, alkyl sulfide, alkyl-aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, alkyl amide, alkyl-aryl amide, alkyl sulfonamide, , alkyl amines, alkyl-aryl amines, alkyl-aryl sulfonamide, alkyl urea, alkyl-aryl urea, alkyl carbamate, alkyl-aryl carbamate, halogen, [hydroxyl amino] hydroxylamino, alkyl carbazate, aryl carbazate;

$R^1 = COR^5$ or $B(OR)_2$, wherein R^5 = H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7,

CF_2R^6, R^6, COR^7 wherein R^7 = H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10} , wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})\ CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, or CH;

W may be present or absent, and if W is present, W is selected from C=O, C=S, SO_2 or C=NR;

Q is $(NR)_p$, O, S, CH_2, CHR, CRR' or a double bond towards V;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_2 , C=O or a bond;

G is $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, NR, O, S, SO_2, $S(O)_2NH$, C=O, or a double bond towards E or V;

V is CH, CR or N;

p is a number from 0 to 6; and

R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; heteroaryl; alkyl-aryl; alkyl-heteroaryl; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms;

with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano,

nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, hydroxamate and thiourea,

with the following provisos:

(i) that when

R^3 = HOOC-CH_2-CH_2-

Z= N

R^4= H

W= >C=O

Y= -CH_2-

X= aryl ether

A= -CH_2-

E is absent

G= -$(CH_2)_p$-, wherein p is 0

Q= -NH-

V= >CH-

and R^2=-COOH,

then R^1 is not a carboxylic acid or carboxylic ester; and

(ii) that when

R^3= H

Z= CH

R^4= H

W, Y, X and E are all absent

A is present or absent

Q= NH

V= CH

R^2=H

R^1= COR^5

R^5= $N(R^9)R^{10}$

R^9= H

R^{10}= $CH(R^1)CONHCH(R^{2'})COOR^{11}$

R^{11}= H

R2'= H, and

R1'= alkylheteroaryl,

then G is absent.

Claim 21 (amended): A [pharmaceutical] composition comprising as an active

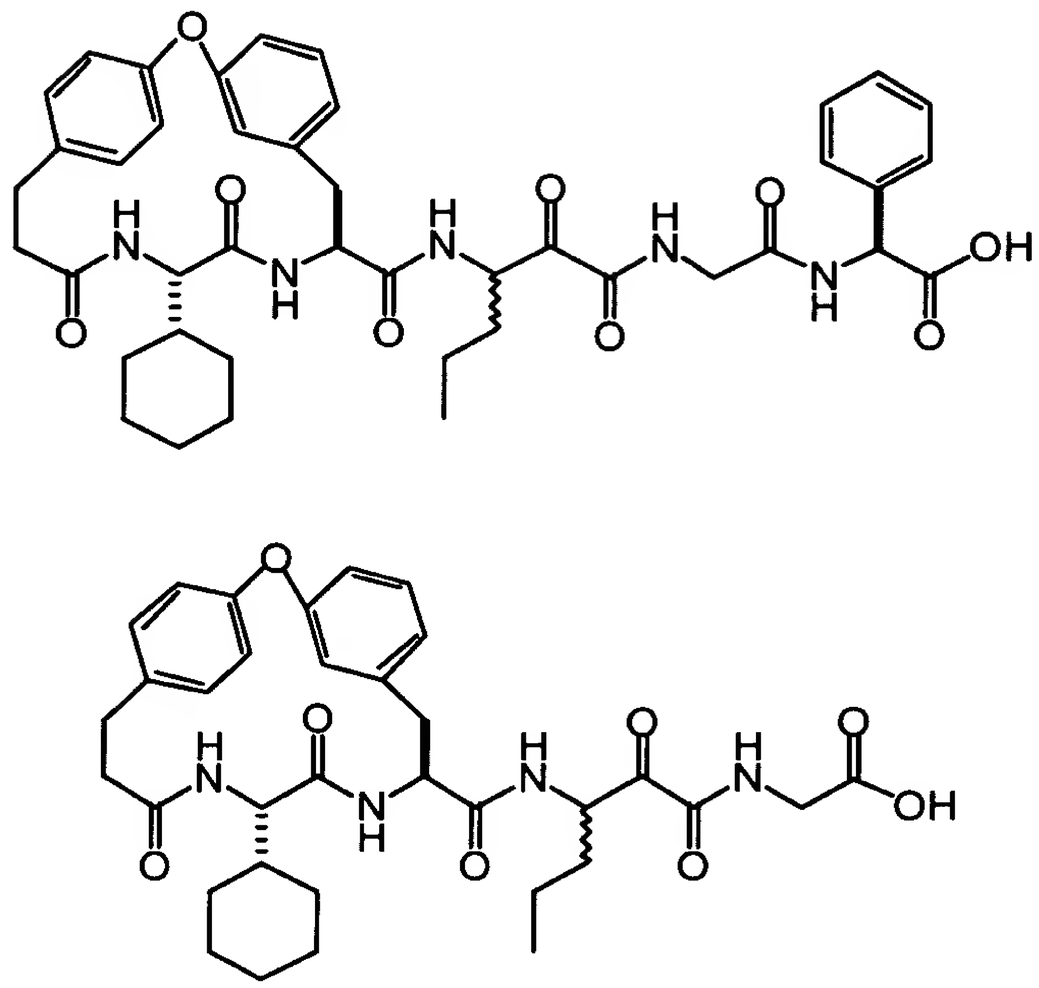
ingredient a compound of claim 1 and a pharmaceutically acceptable carrier.

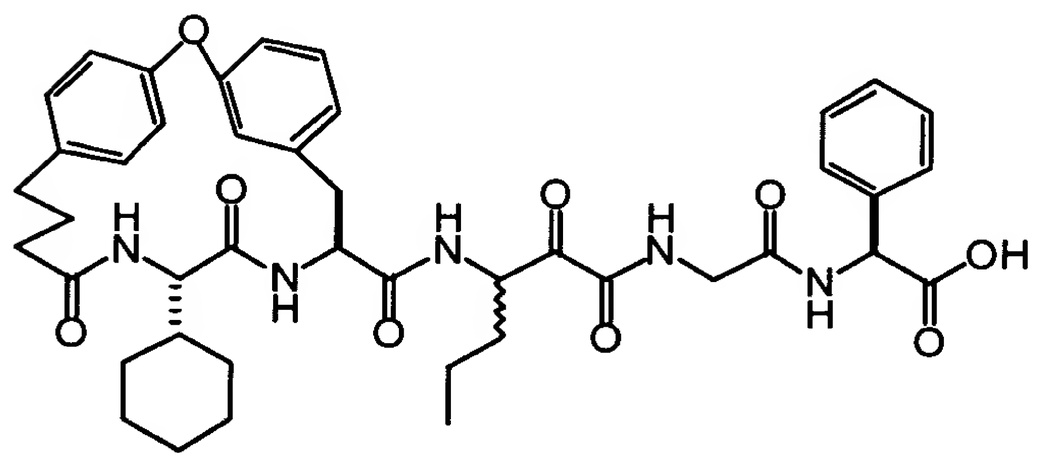
Claim 22 (amended): The [pharmaceutical] composition of claim 21 [for use in treating disorders associated with Hepatitis C virus] wherein said compound of claim 1 is present in amounts effective to inhibit hepatitis C nonstructural protein-3 protease (HCV NS3 protease).

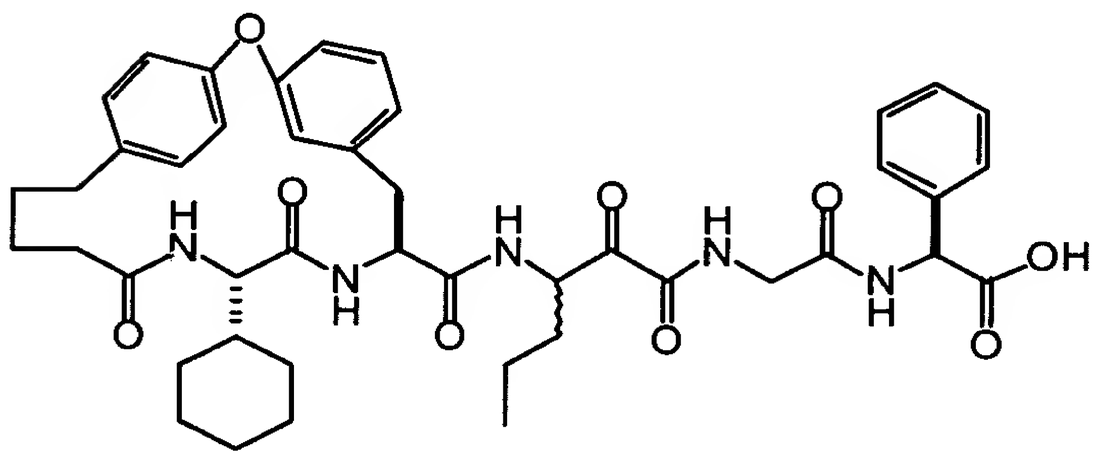
Please cancel Claim 23 without prejudice.

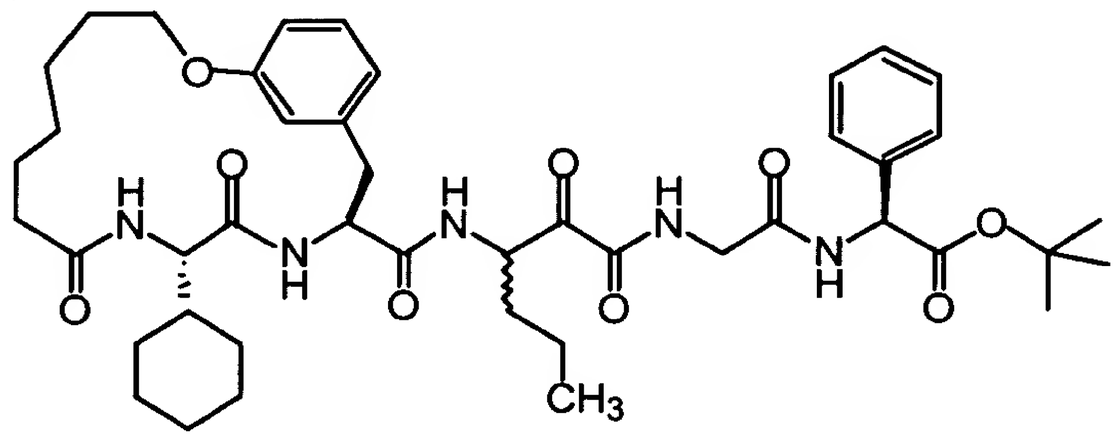
claim 26 (amended): A method of preparing a [pharmaceutical] composition for [treating disorders associated with the HCV protease] inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease), said method comprising bringing into intimate contact a compound of claim 1 in an amount effective to cause said inhibition and a pharmaceutically acceptable carrier.

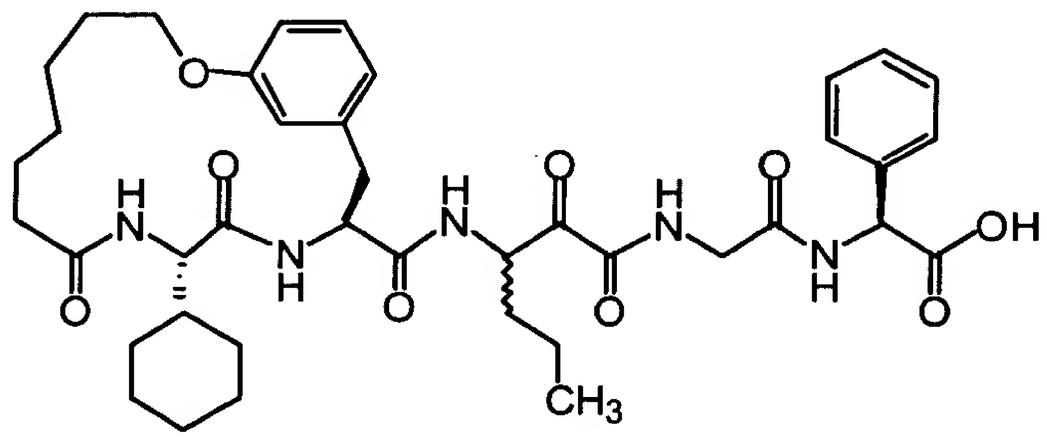
Claim 27 (amended): A compound exhibiting [HCV protease] HCV NS3 protease inhibitory activity, [including] or enantiomers, stereoisomers, rotamers [and] or tautomers of said compound, [and] or pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the group of compounds with structures listed below:

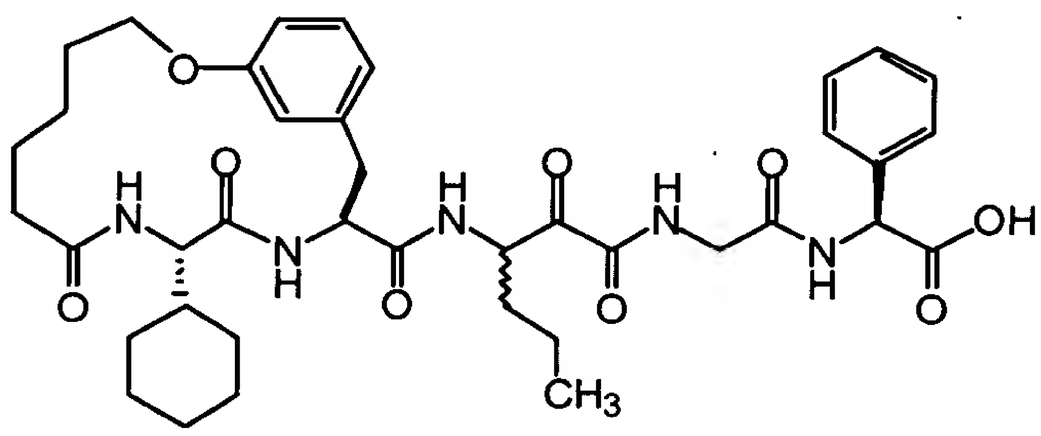


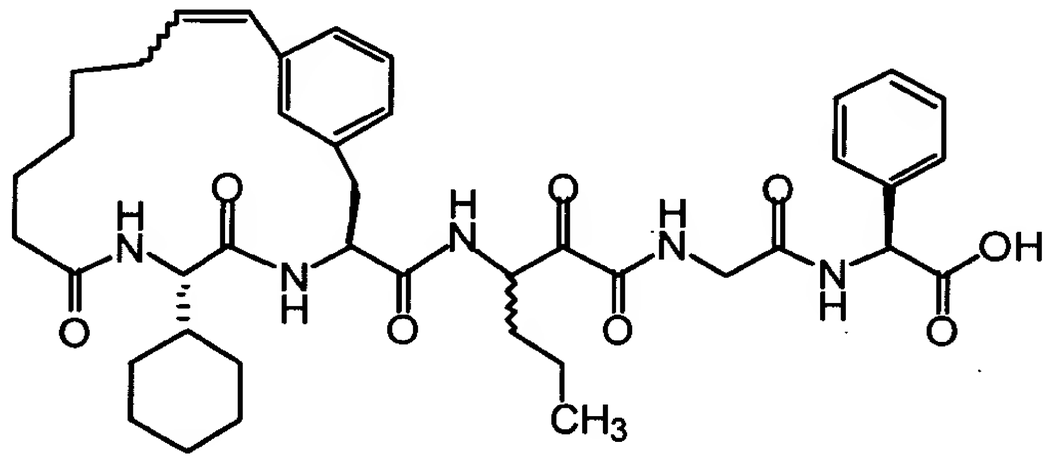


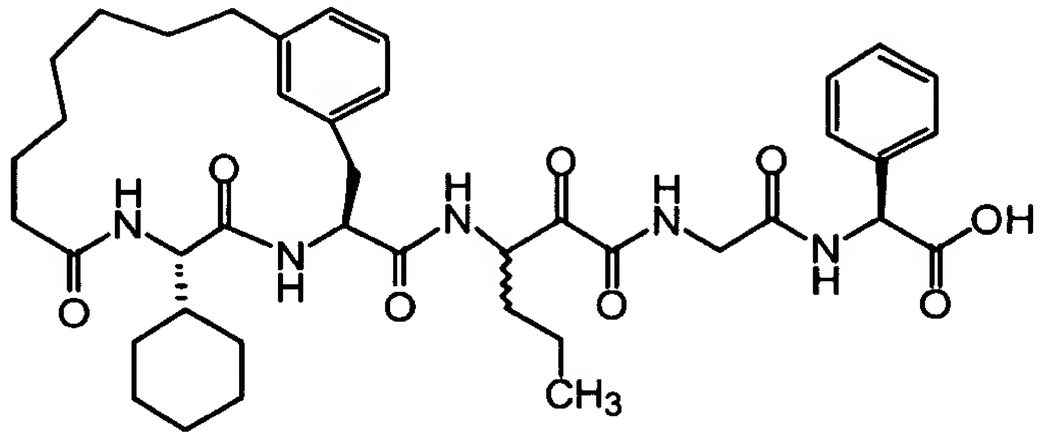


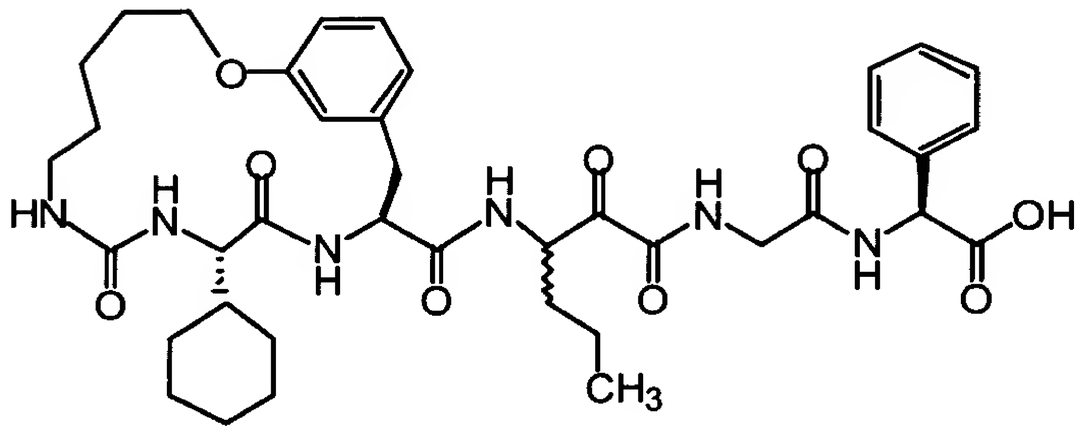


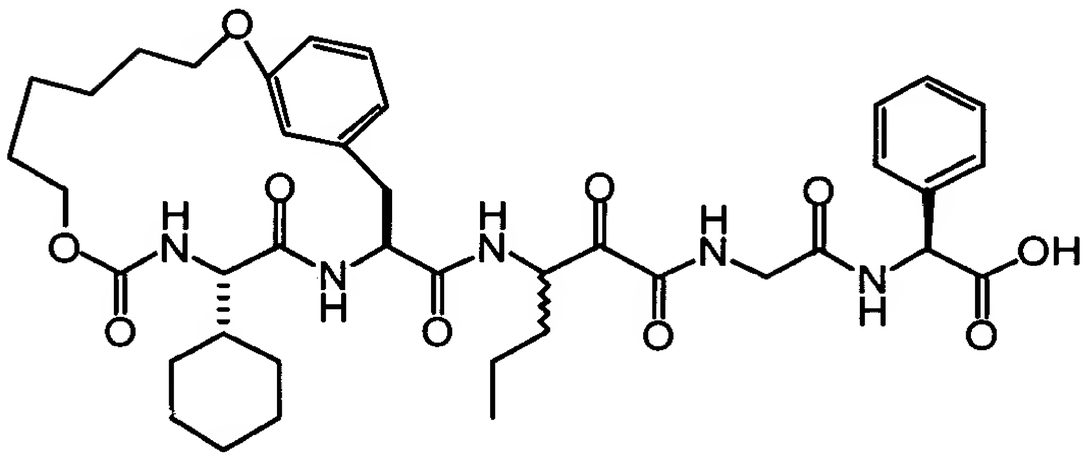


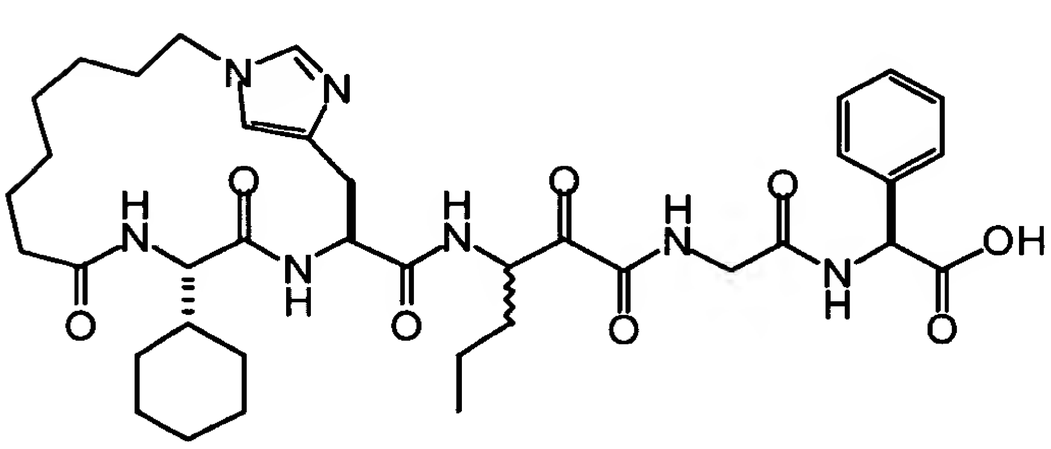


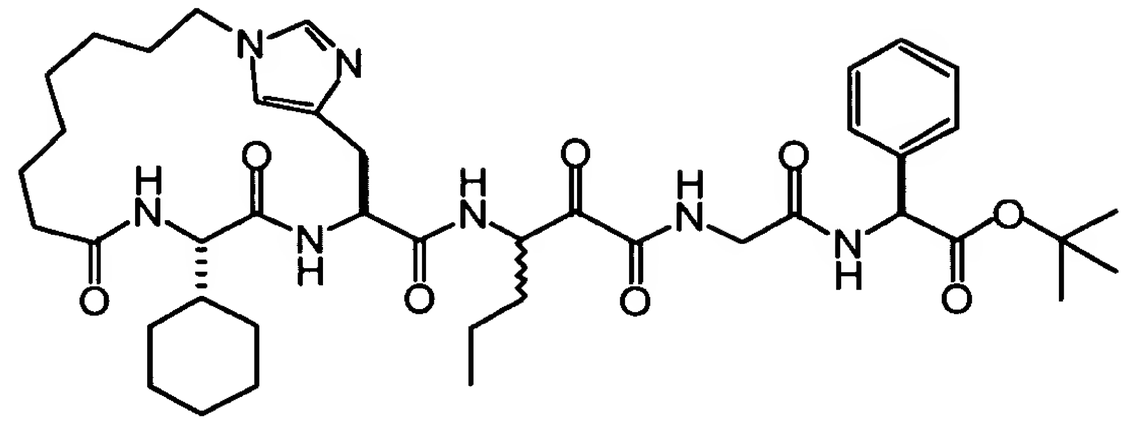


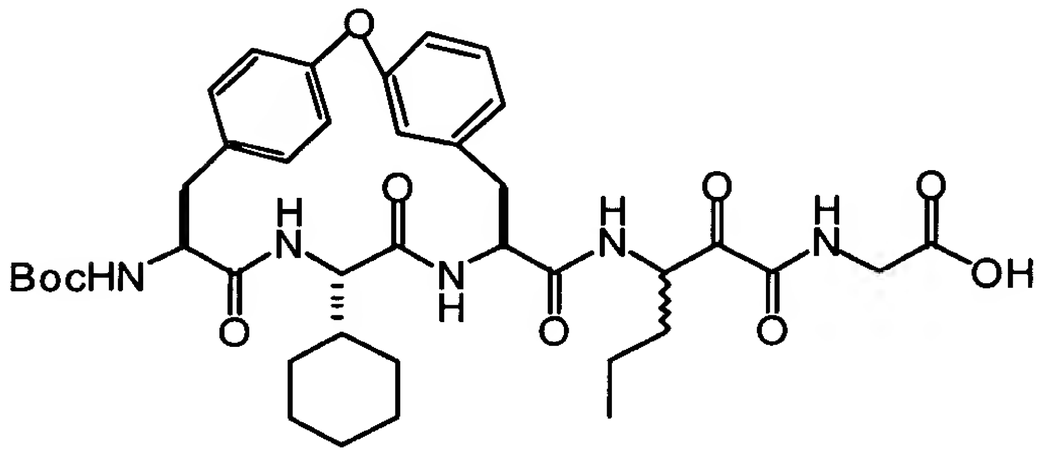








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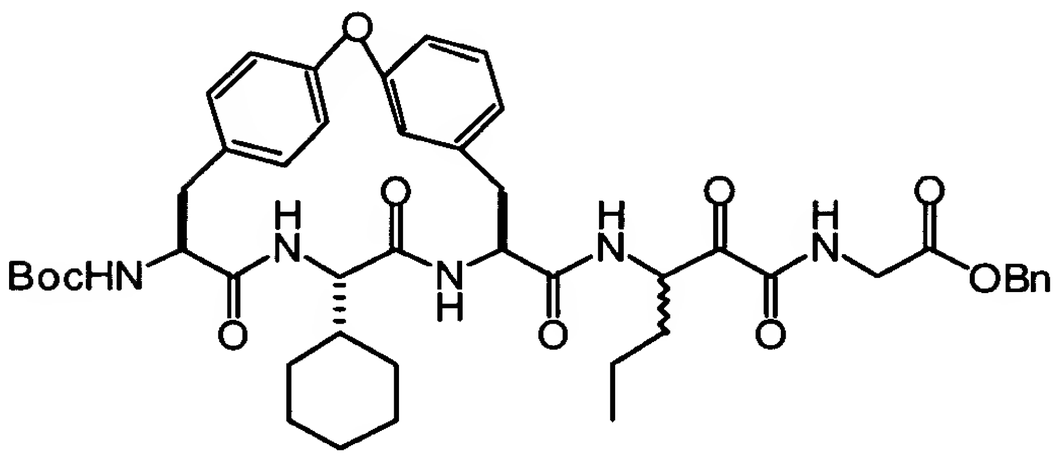
OH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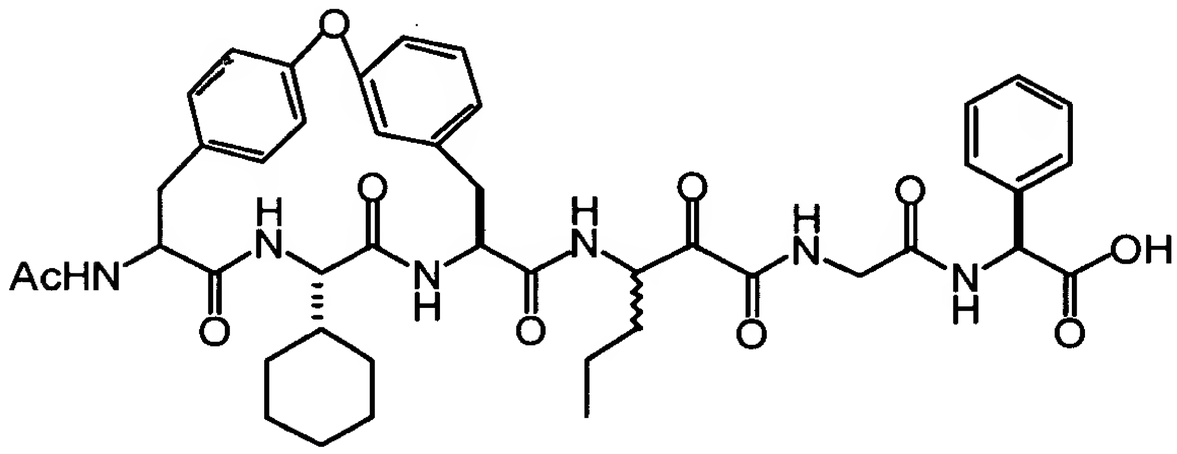
OBn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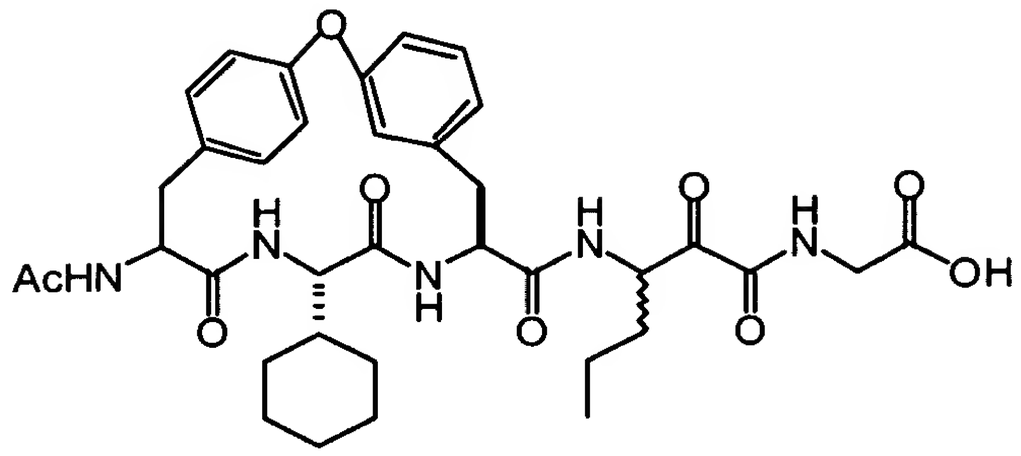
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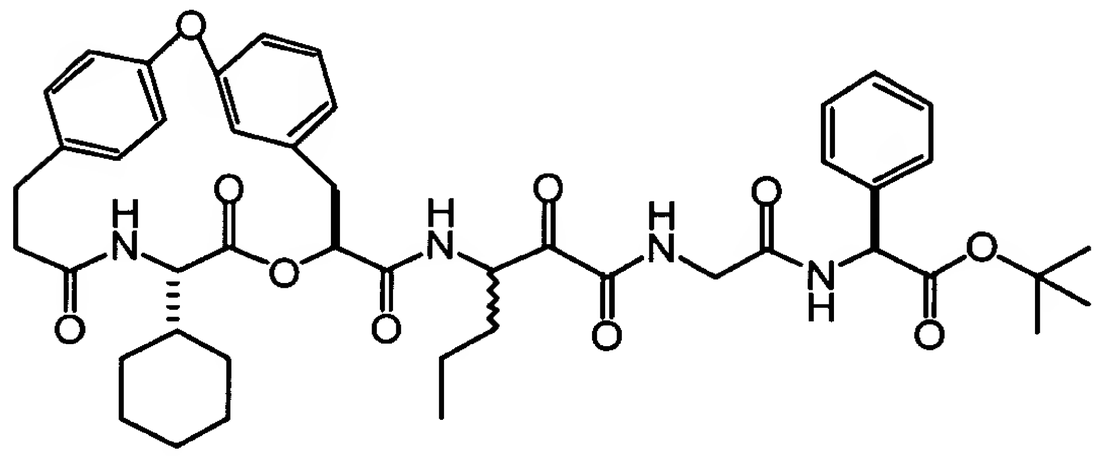
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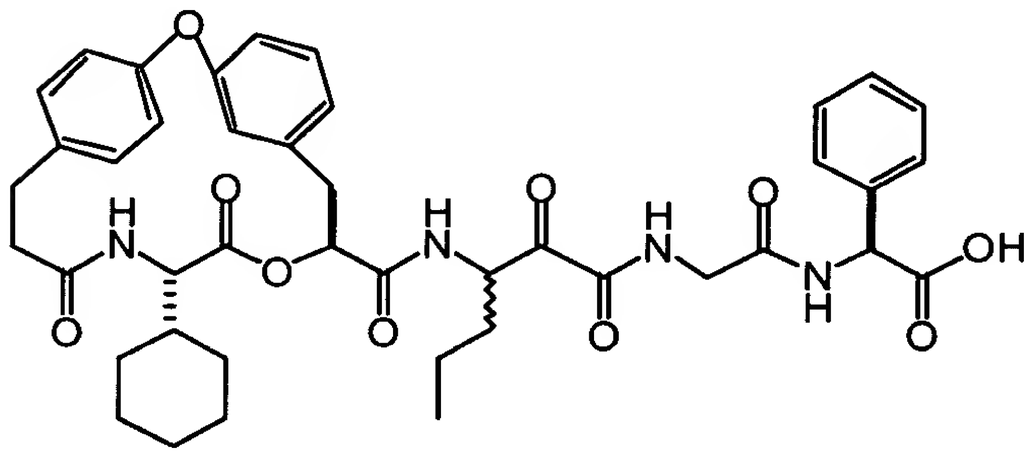
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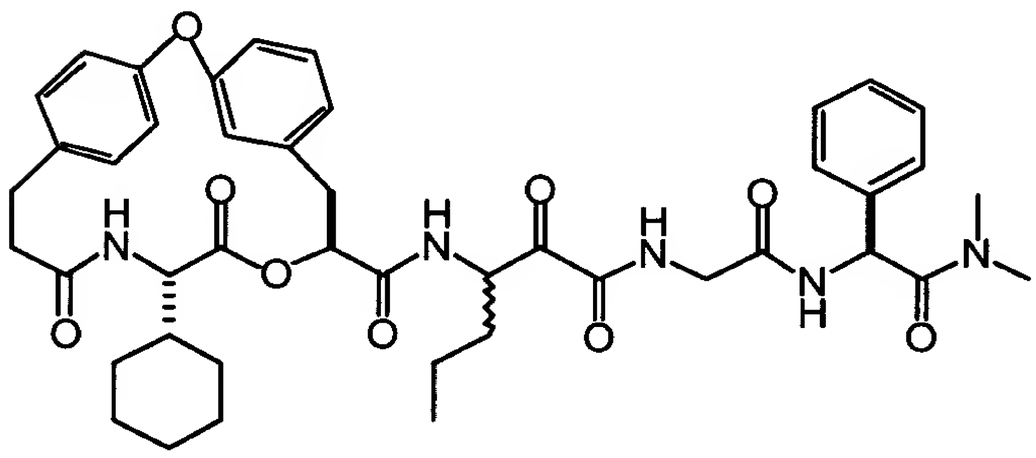
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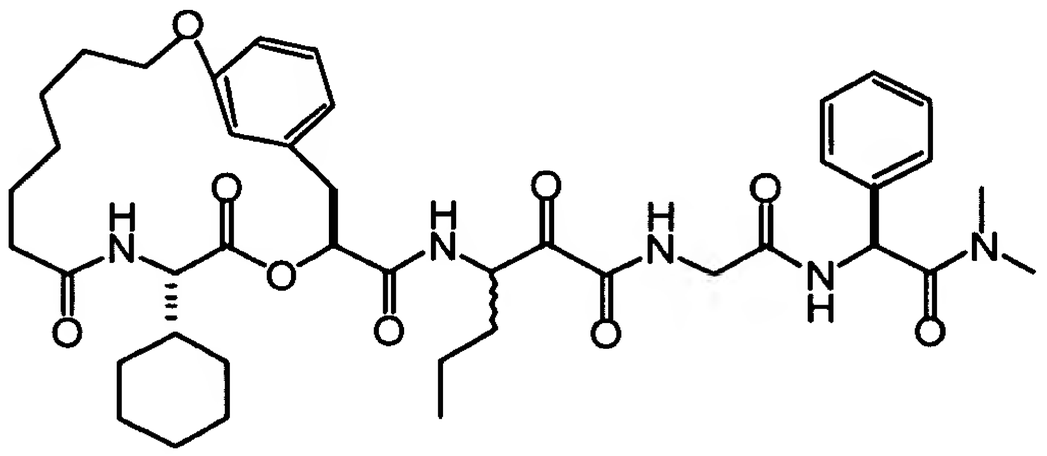

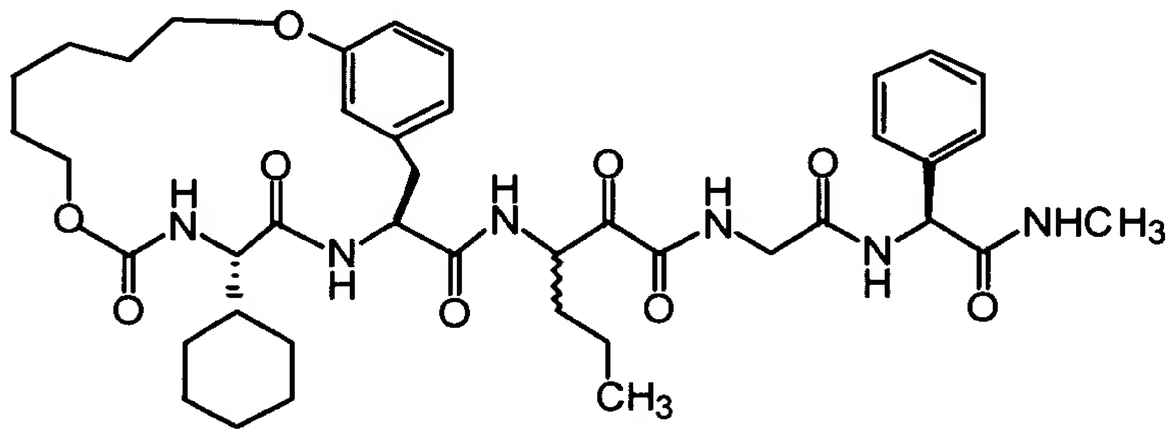

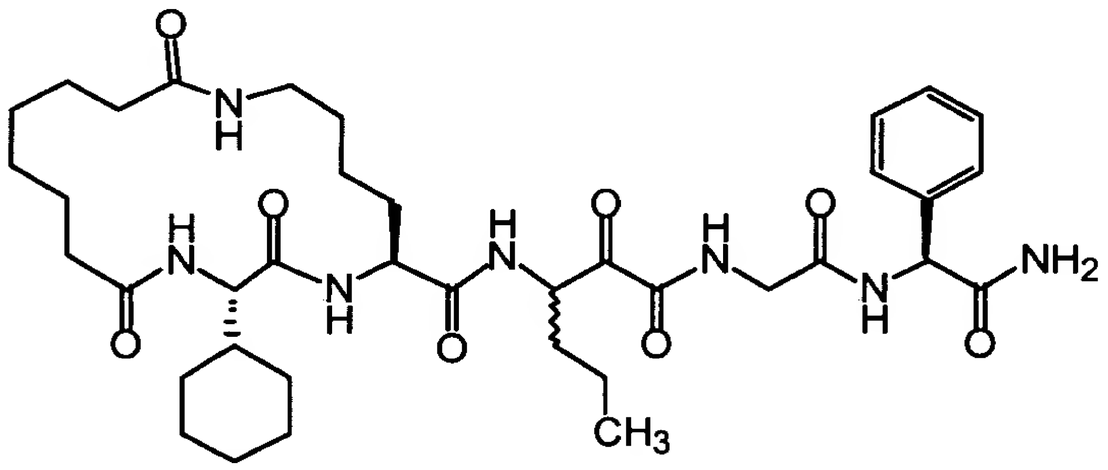

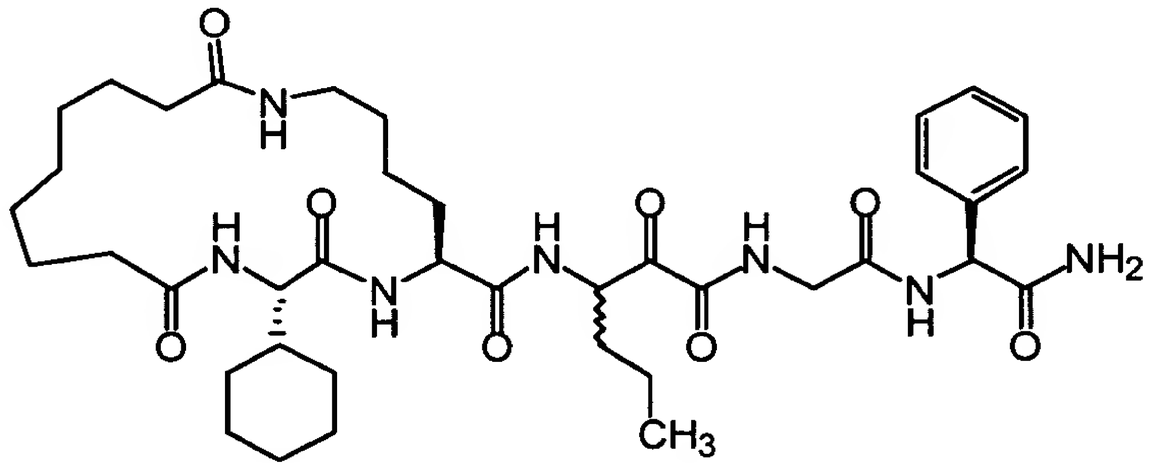

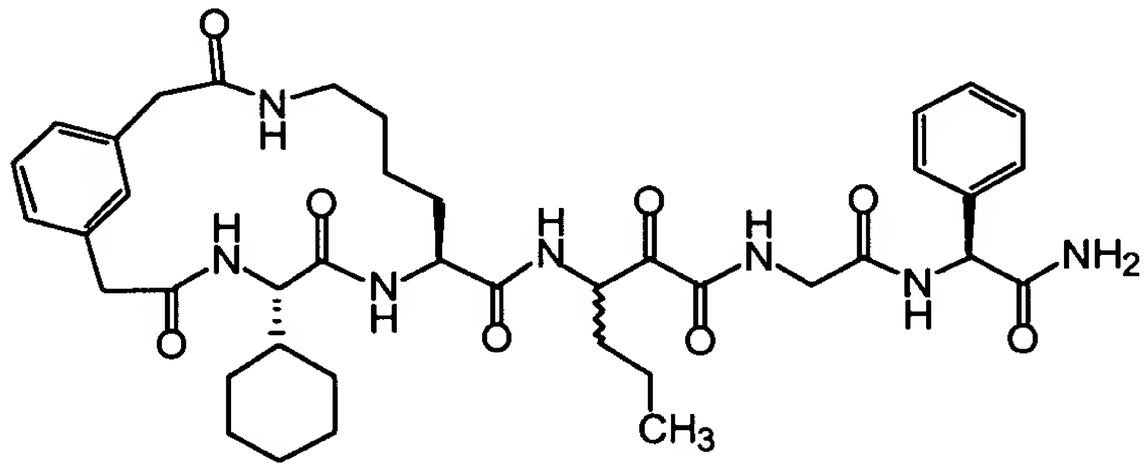

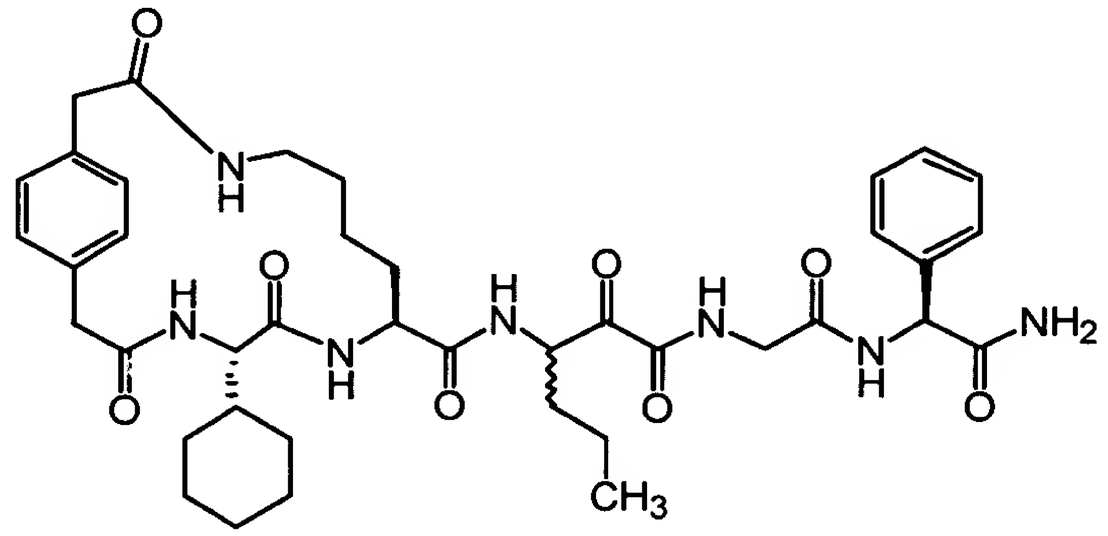

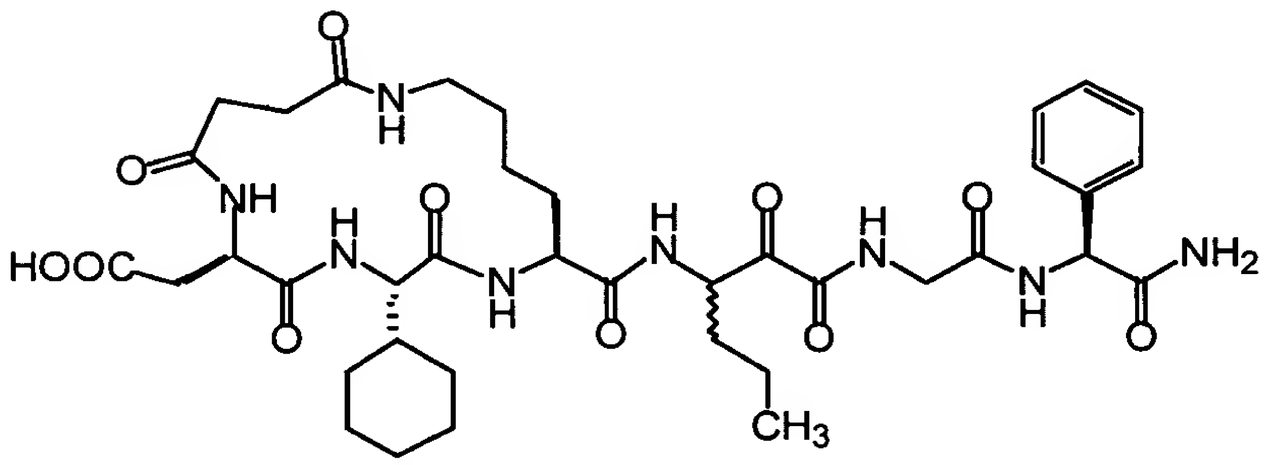

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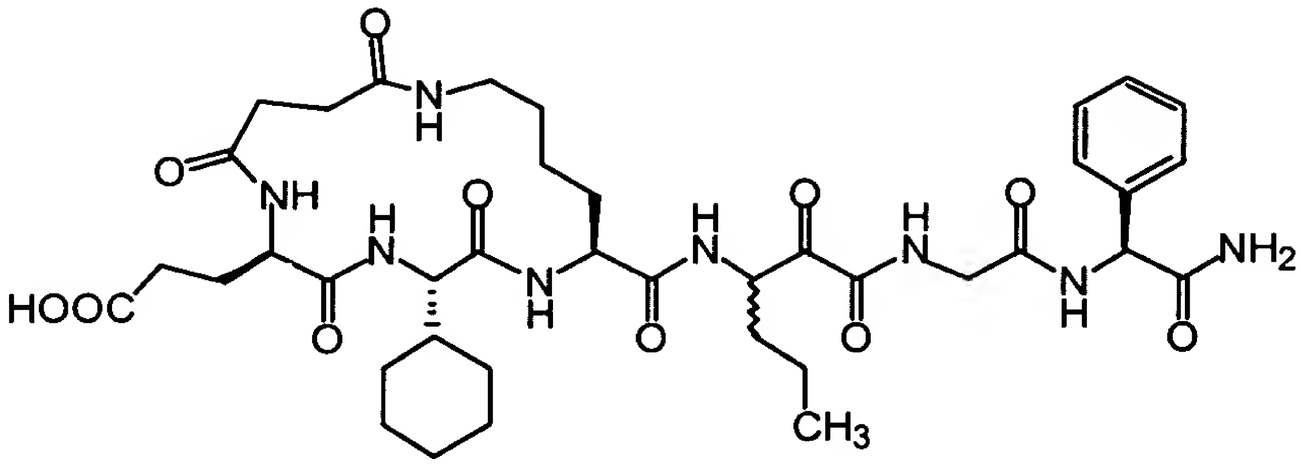

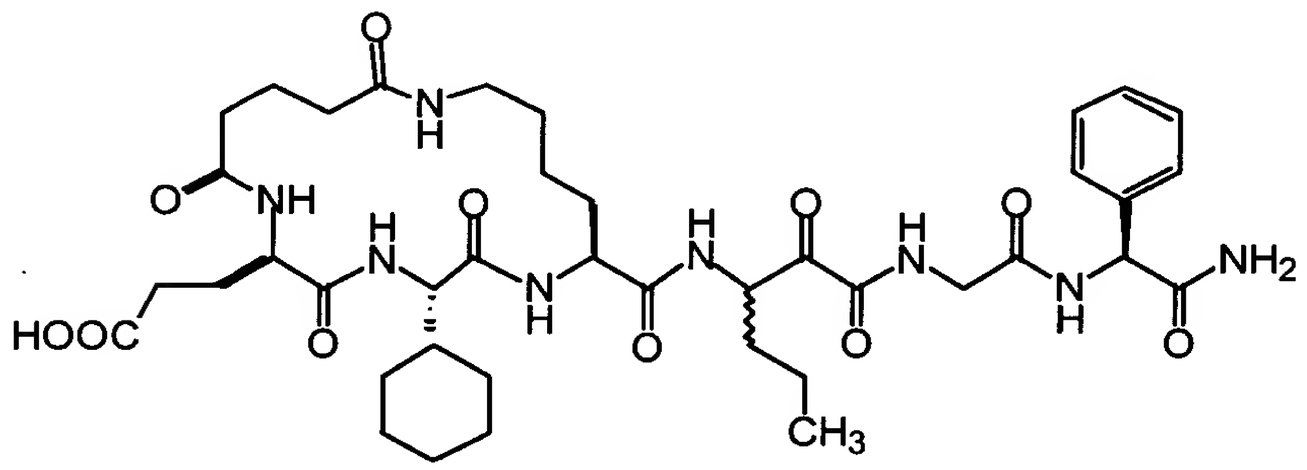

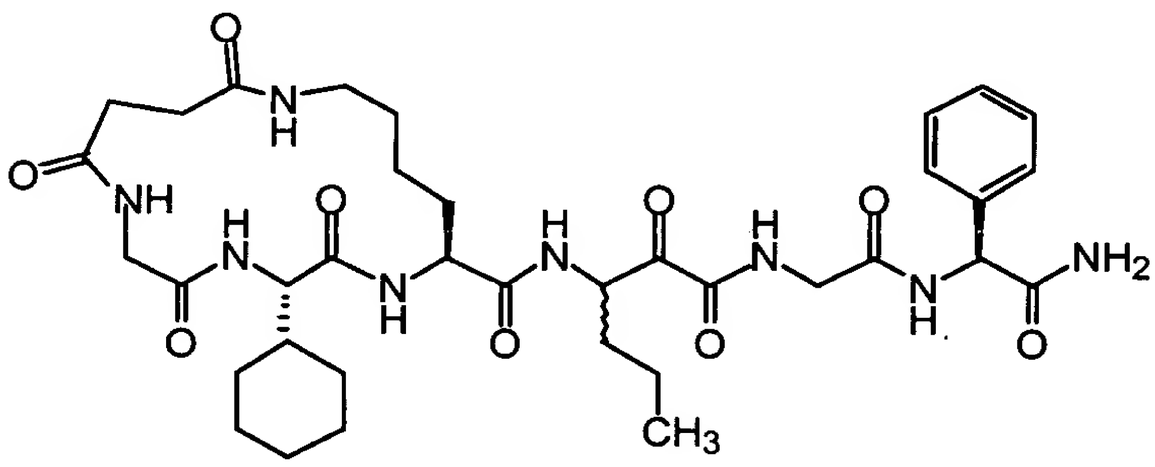

Claim 28 (amended): A [pharmaceutical] composition for [treating disorders associated with the HCV protease] inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease), said composition comprising [therapeutically effective amount of] one or more compounds in claim 27 in amounts therapeutically effective to cause said inhibition and a pharmaceutically acceptable carrier.

Claim 29 (amended): The [pharmaceutical] composition of claim 28, additionally containing an antiviral agent.

Claim 30 (amended): The [pharmaceutical] composition of claim 28 or claim 29, still additionally containing an interferon.

Claim 31 (amended): The [pharmaceutical] composition of claim 30, wherein said antiviral agent is ribavirin and said interferon is α-interferon.

Claim 32 (new claim): A method of inhibiting HCV NS3 protease comprising administering a compound of claim 1 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.

Claim 33 (new claim): A method of inhibiting HCV NS3 protease comprising administering a composition of claim 21 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.

Claim 34 (new claim): A method of inhibiting HCV NS3 protease comprising administering a compound of claim 27 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.

Claim 35 (new claim): A method of inhibiting HCV NS3 protease comprising administering a composition of claim 28 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.

Claim 36 (new claim): A method of inhibiting hepatitis C virus replication comprising administering a compound of claim 1 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.

Claim 37 (new claim): A method of inhibiting hepatitis C virus replication comprising administering a composition of claim 21 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.

Claim 38 (new claim): A method of inhibiting hepatitis C virus replication comprising administering a compound of claim 27 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.

Claim 39 (new claim): A method of inhibiting hepatitis C virus replication comprising administering a composition of claim 28 to a patient in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.